

REMARKS

Claims 25, 27 and 45-70 are currently pending. Claim 60 has been amended. No claim has been allowed.

Objections

The Action objected to the title because the title of the invention is allegedly not aptly descriptive. The title has been amended.

The Action also objected to the abstract of the disclosure because it is allegedly not directed to the claimed invention. The abstract has been amended.

The Action objected to "improper" references to unpublished patent applications. U.S. Patent Application Serial No. 09/096,631 is a co-pending application assigned to Osteoscreen, Inc. Both essential and nonessential subject matter may be incorporated by reference to prior filed, commonly owned U.S. applications. MPEP § 608.01(p)(I)(A). Osteoscreen is the common owner of the instant application and the co-pending Application Serial No. 09/096,631. Therefore, the co-pending application has been properly incorporated by reference. In addition, the reference of U.S. Patent Application Serial No. 09/096,631 at page 4, lines 13-14 and at page 26, lines 4-5 has been replaced with a reference of U.S. Patent No. 6,080,779, which issued from U.S. Patent Application Serial No. 09/096,631.

In light of the above remarks, Applicants respectfully submit that the objections to the specification have been overcome. Therefore, Applications request the withdrawal of the objections.

Obviousness-Type Double Patenting Rejection

Claims 25 and 45-70 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1 and 7-13 of the copending Application Serial No. 09/361,775.

Applicants will submit a terminal disclaimer once allowable subject matter is indicated in the present application.

Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 25 and 45-70 are rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to reasonably provide enablement for “a compound that inhibits proteasomal activity, inhibits the chymotrypsin like activity of the proteasome.” The Examiner asserts that “high throughput screening is mentioned but does not state for what the compounds were screened.” According to the Action, no meaningful or statistically significant data regarding the effects of the compounds is provided in any example “especially as claimed in the present claims 64, 68, 70 and others.” The Examiner then states that a large proportion of inoperative compounds have been claimed, insufficient guidance has been provided to predict which substances encompassed by the claims would work, the extension of working examples to other compounds has not been specifically taught or suggested, the nature of the invention is complex and unpredictable, the state of the prior art indicates that most related substances are not effective for the claimed functions, the level of predictability in the art is very unpredictable, the breadth of the claims encompasses an innumerable number of compounds, and the level of one of ordinary skill in the art is variable. Applicants respectfully traverse this rejection.

Written description

Applicants respectfully submit that the instant specification provides complete written description for all of the claimed features. First, the specification teaches the use of a high throughput method used to identify the claimed compounds in Example 1, page 34. A person of skill in the art would recognize the use of the 2T3-BMP-2-LUC cells as an assay to screen compounds for osteogenic/hair growth activity in light of the disclosure in Example 1 and page 19, line 6 - page 20, line 10 (ABA Screening Assay). Second, meaningful data is provided in the Examples using *in vitro* murine skin cultures and *in vivo* murine models, animal model assays

recognized in the art as a correlate to the use of the claimed method for a human. According to the MPEP § 2164.02, “if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate.” These assays provide adequate enablement for the method of claim 64. Third, complete written description regarding the various hair growth parameters of claim 68 is found at page 9, line 6-12; page 15, line 25-29; and Examples 8-16. Fourth, complete written description regarding the agent of claim 70 is found on page 2, line 30 to page 3, line 4 and page 12, lines 2-5.

Enablement

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with the information known in the art without undue experimentation. *United States v. Telecommunications, Inc.*, 8 U.S.P.Q.2d 1217 (Fed. Cir. 1988). The instant specification discloses and teaches the methods for identifying compounds to be used in the claimed method, exemplary compounds having the disclosed characteristics, and working examples demonstrating the use of the claimed invention. Furthermore, following the teachings of the instant specification, Applicants have conducted more experiments demonstrating the use of various proteasome inhibitors in stimulating hair growth. *See Exhibit B.*

In particular, Applicants have demonstrated the effects of PSI *in vivo* to achieve statistically significant increases in the number of active hair follicles (Exhibit B, paragraph 4) and in the overall follicle area in the skin (Exhibit B, paragraph 5). The remarkable efficacy of PSI in stimulating hair growth is illustrated grossly and histologically at Exhibit B, Figures 6-12. Applicants have also demonstrated the hair growth-stimulating effects of other compounds disclosed in the instant specification at pages 27-28. Specifically, Applicants have demonstrated increased hair growth following treatment with epoxomicin, MG132, lactacystin, MG 115, and calpain inhibitor 1. *See Exhibit B*, paragraphs 5 and 8, figures 3 -5, and Table 1. In addition, it

is known in the art that epoxomicin inhibits the chymotrypsin-like activity of proteasome (See e.g., Exhibit K, Meng et al., *Proc. Natl. Acad. Sci. U.S.A.*, 96(18):10403-8 (1999)).

Applicants respectfully submit that the scope of the claims is fully enabled by the instant specification. Applicants have provided working examples using PSI as well as a list of compounds known to be inhibitors of proteasomal activity. To limit the scope of the claims to the compounds listed in the actual working examples is to require actual reduction to practice prior to the filing of a patent application, which is contrary to legal precedent. *See Gould v. Quigg*, 2 U.S.P.Q.2d 1302, 1304 (Fed. Cir. 1987) (an applicant need not have actually reduced the invention to practice prior to filing). Moreover, the data provided in Dr. Mundy's declaration demonstrates the efficacy of five additional compounds with diverse chemical structures disclosed in the instant specification, establishing that the instant disclosure provides adequate direction or guidance to predict which substances encompassed by the claims would work. Applicants respectfully submit that the Examiner has not provided data showing that a large proportion of the claimed compounds are inoperative or why the amount of direction or guidance is insufficient to determine which compounds would work. According to the MPEP § 2144.03,

When a rejection is based on facts within the personal knowledge of the examiner, the data should be stated as specifically as possible, and the facts *must* be supported, when called for by the applicant, by an affidavit from the examiner. (emphasis added).

Thus, Applicants respectfully request the Examiner to present factual support for the assertion that a large proportion of inoperative compounds are claimed and that the amount of direction or guidance is insufficient to determine which compounds would work according to MPEP § 2144.03.

The extension of the teaching of the examples to other compounds is taught throughout the instant specification. Applicants disclose other compounds known to be proteasomal inhibitors that stimulate an increase in the number of hair follicles in addition to PSI. To a person of skill in the art, the inclusion of these additional compounds with effective doses

disclosed would unmistakably convey an extension of the teaching of the examples to other compounds with similar proteasomal inhibitory properties. Moreover, the data provided in Dr. Mundy's declaration definitively demonstrates the efficacy of these compounds in stimulating hair growth. *See Exhibit B*, paragraphs 5 and 8, figures 3 -5 and Table 1.

The Examiner also alleges that the nature of the invention is complex and unpredictable, that most related substances are not effective for the claimed functions, that the level of predictability in the art is very unpredictable, that an innumerable number of compounds, and that the level of ordinary skill in this art is variable are encompassed by the breadth of the claims without providing specific reasons or data to support these allegations. Again,

[w]hen a rejection is based on facts within the personal knowledge of the examiner, the data should be stated as specifically as possible, and the facts *must* be supported, when called for by the applicant, by an affidavit from the examiner. (emphasis added).

MPEP § 2144.03. Thus, Applicants respectfully request the Examiner to present factual support for these allegations according to MPEP § 2144.03.

In light of the above arguments, Applicants respectfully submit that the rejection of claims 25 and 45-70 under 35 U.S.C. § 112, first paragraph, has been overcome. Therefore, Applicants request the withdrawal of this rejection.

Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 25 and 45-70 are rejected under 35 U.S.C. 112, second paragraph, for allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. According to the Action, the compound in claim 25 is described in functional terms only. Applicants respectfully traverse this rejection.

Applicants respectfully submit that “[f]unctional language does not, in and of itself, render a claim improper.” MPEP § 2173.05(g), *citing In re Swinehart*, 439 F.2d 210, 169 U.S.P.Q. 226 (C.C.P.A. 1971). A claim limitation is definite as long as those skilled in the art

would understand what is claimed when the claim is read in light of the specification and the claim language is as precise as the subject matter permits. *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 1 U.S.P.Q.2d 1081 (Fed. Cir. 1986).

The functional limitations in the instant claims convey to a person of skill in the art the metes and bounds of the invention using functional characteristics. The presently claimed methods are definite because what constitutes proteasomal inhibitors are known in the art. For example, various proteasomal inhibitors with diverse chemical structures, such as indanone compounds (Exhibit C, U.S. Patent No. 6,117,887), α -ketoamide inhibitors of 20S proteasome (Exhibit D, U.S. Patent No. 6,075,150), a carboxy-terminal fragment of a protein activator PA28 (Exhibit E, U.S. Patent No. 5,847,076), 2-aminobenzylstatine derivative I (Exhibit F, Furet et al., *Bioorg. Med. Chem. Lett.*, 11(10):1321-4 (2001)), PS-341 (Exhibit G, Sunwoo et al., *Clin. Cancer Res.*, 7(5):1419-28 (2001)), dipeptidyl proteasome inhibitor, phthalimide-(CH₂)₈CH-(cyclopentyl) CO-Arg(NO₂)-Leu-H (CEP1612) (Exhibit H, Sun et al., *Cancer Res.*, 61(4):1280-4 (2001)), and 4-hydroxy-5-iodo-3-nitrophenylacetyl-Leu-Leu-leucinal-vinyl sulfone (NLVS) (Exhibit I, Princiotta et al., *Proc. Natl. Acad. Sci. U.S.A.*, 98(2):513-8 (2001)), are known in the art. In addition, these functional characteristics of inhibition of proteasomal activity, or the production of these proteins are taught in the present specification, known in the art and are readily and definitively determinable by one skilled in the art using standard assays. *See e.g.*, Exhibit J, U.S. Patent No. 5,693,617, which discloses testing methods for determining whether given candidate compounds are effective for inhibiting proteasomal activity. Therefore, one skilled in the art could readily identify the compounds within the scope of the instant claims.

Moreover, the claims contain numerous and explicit functional limitations and specific structures (*See e.g.*, claims 47-63). Therefore, one skilled in the art could readily identify the compounds within the scope of the instant claims.

The Action further requests that the names of the compounds in claim 60 should be spelled out.

Applicants have amended claim 60 to spell out the names of the compounds, as requested by the Examiner.

In light of the above arguments, Applicants respectfully submit that the rejection of claims 25 and 45-70 under 35 U.S.C. § 112, second paragraph, for alleged indefiniteness has been overcome. Therefore, Applicants request the withdrawal of this rejection.

Rejection Under 35 U.S.C. § 103(a)

Claims 25, 45-59 and 61-70 are rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Murase. Claim 60 is rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Murase in view of Fenteany.

According to the Action, Murase teaches an NF- κ B activation inhibitor which prevents degradation or breakdown of corium constituents for treating skin conditions. The Examiner argues that it would have been obvious to one of ordinary skill at the time the invention was made to stimulate hair growth with “the method of Murase which prevents degeneration of corium constituents because degeneration of the corium would be detrimental to hair growth.” The Action also asserts that Fenteany teaches that lactacystin and analogs are selective for proteasomes. According to the Examiner, it would have been obvious to one of ordinary skill in the art at the time the invention was made to “employ lactacystin or a peptidyl aldehyde as a proteasomal inhibitor in the method of Murase because Fenteany teaches that lactacystin is a proteasomal inhibitor.”

The Examiner acknowledges two distinctions between the instant claims and Murase. First, the instant claims differ in that they are directed to stimulating hair growth specifically. Second, the instant claims differ in that they are directed to lactacystin or a peptidyl aldehyde specifically.

Applicants respectfully traverse these rejections.

1. **The use of an NF- κ B inhibitor to prevent degeneration of the corium does not make obvious the use of an proteasomal inhibitor to stimulate hair growth.**

Murase, which allegedly teaches the use of an NF- κ B activation inhibitor to prevent degradation or breakdown of corium constituents for treating skin conditions, is totally irrelevant as to claims 25 and 45-70 because proteasomal inhibitors, not NF- κ B activation inhibitors, are used in these claims. Similarly, Fenteany, which allegedly teaches that lactacystin and analogs are selective for proteasomes, does not teach the use of lactacystin and its analogs to stimulate hair growth. Therefore, it is respectfully submitted that claims 25 and 45-70 are not obvious over Murase alone, or Murase in view with Fenteany.

2. There is no motivation to combine the teachings of Murase and Fenteany.

There is no suggestion to combine the cited references to stimulate hair follicle growth. “There must be some suggestion for [combining prior art references] found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art.” *In re Jones*, 21 U.S.P.Q.2d 1941, 1943-44 (Fed. Cir. 1992). “The mere fact that the references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination.” MPEP § 2143.01 (citing *In re Mills*, 916 F.2d 680, 16 U.S.P.Q.2d 1430 (Fed Cir. 1990)) (emphasis included).

Applicants respectfully submit that nothing in Murase or Fenteany suggests the desirability of combining these references to teach or suggest the use of proteasomal inhibitors to stimulate hair growth. It is not obvious that a compound can stimulate proliferation when a compound is known to be growth inhibitory and pro-apoptotic. Murase teaches the use of NF- κ B inhibitors to prevent or ameliorate itching (pruritis), skin thickening (pachymenia), blistering (epidermolysis), disorder of skin texture, pigmentation, or skin chopping. Therefore, Murase appears to teach that NF- κ B inhibitors can be used to effectively treat disorders involving keratinocytes and perhaps melanocytes. However, Murase does not teach or suggest the use of NF- κ B inhibitors to *stimulate* hair growth. In fact, Murase *teaches away* from the use of NF- κ B inhibitors as *growth promoters* by teaching the use of NF- κ B inhibitors to prevent or ameliorate skin thickening because such an inhibitor would be anti-proliferative. This teaching would

suggest to a person of skill in the art that NF- κ B does not function as a growth promoting agent in the skin, much less in the hair follicle itself.

Fenteany teaches the use of lactacystin in muscle wasting diseases, cachexia, inhibition of antigen presentation, transplant rejection, Alzheimer's disease, cyclin-related inflammation, and proliferative diseases (such as cancer, psoriasis, or restenosis). Fenteany teaches the ability of proteasomal inhibitors as growth inhibitory in, for example, lymphocytes (transplant rejection), skin (psoriasis), and heart (restenosis). In other words, Fenteany teaches using proteasomal inhibitors in disease states where cellular proliferation is uncontrolled or contraindicated, such as cancer and psoriasis, or in disease states where degradation of proteins is uncontrolled, such as muscle wasting or hepatic failure. As with Murase, the ability to inhibit cellular proliferation or protein degradation does not make the ability to induce cellular proliferation obvious to one of ordinary skill in the art. In fact, knowledge of such effects would *teach away* from the use of such compounds to elicit proliferative responses in other cell populations. In addition, Fenteany neither teaches nor suggests the desirability of using proteasomal inhibitors for hair growth.

3. Murase in view of Fenteany fails to teach every element of the claimed methods

A combination of references must teach every element of the invention. MPEP § 706.02(j). Murase in view of Fenteany fails to teach the critical element of stimulating hair growth, and thus, do not make the instant invention obvious. Therefore, Applicants respectfully submit that there is no motivation to combine the teachings of Murase with Fenteany for use of proteasomal inhibitors in stimulating hair growth and the teachings of Murase and Fenteany, even combined, do not teach each and every element of the presently claimed methods. In addition, claims 27¹ and 45-63 contain additional limitations as to the proteasomal inhibitors

¹ The Office Action stated that only claims 25 and 45-70 are pending and omitted pending claim 27. Claim 27, however, is still pending in the present application. See Preliminary Amendment filed with the present application at pages 2 and 8.

used in the present methods. Murase and Fenteany, whether alone or in combination, fail to teach these additional limitations.

In light of the above arguments, Applicants respectfully submit that the rejection of claims 25 and 45-70 under 35 U.S.C. § 103(a) has been overcome. Therefore, Applicants request the withdrawal of this rejection.

CONCLUSION

Applicants respectfully submit that the rejections under 35 U.S.C. §§ 112 and 103 have been overcome by the above remarks and/or amendments. Early allowance of the pending claims 25 and 45-70 is respectfully requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. 432722002612.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

At page 1, lines 1-2, please amend the title as follows:

INHIBITORS OF PROTEASOMAL ACTIVITY FOR STIMULATING [BONE AND
]HAIR GROWTH.

At page 1, after the title, lines 4-8, please amend the first paragraph as follows:

This application is a divisional of U.S. Serial No. 09/695,807, filed October 23, 2000, now pending, which is a continuation-in-part of U.S. Serial No. 09/421,545, filed 20 October 1999, now pending, which is a continuation-in-part of U.S. Serial No. 09/361,775, filed 27 July 1999, now [pending] U.S. Patent No. 6,410,512 B1, which is a continuation-in-part of U.S. Serial No. 09/113,947, filed 10 July 1998, now pending. The contents of these applications are incorporated herein by reference.

At page 4, please amend the paragraph at lines 8-16 as follows:

Small molecules which are able to stimulate bone formation have been disclosed in PCT applications WO98/17267 published 30 April 1998, WO97/15308 published 1 May 1997 and WO97/48694 published 24 December 1997. These agents generally comprise two aromatic systems spatially separated by a linker. In addition, PCT application WO98/25460 published 18 June 1998 discloses the use of the class of compounds known as statins in enhancing bone formation. U.S. [application Serial No. 09/096,631 filed 12 June 1998] Patent No. 6,080,779 is directed to compounds for stimulating bone growth that are generally isoprenoid pathway inhibitors. The contents of this application, as well as that of the PCT applications cited above, are incorporated herein by reference.

At page 26, please amend the paragraph at lines 1-6 as follows:

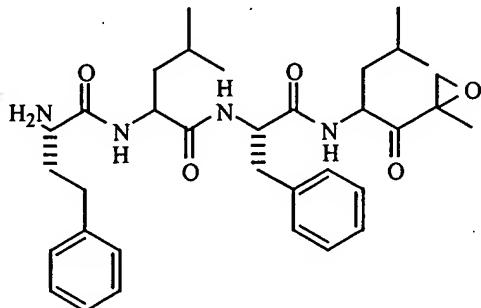
The compounds thus identified, which are used according to the method of the invention as it relates to treating bone defects, however, preferably do not include compounds that inhibit the isoprenoid pathway, such as the statins. A description of these excluded compounds can be found in WO98/25460 and in U.S. [Serial No. 09/096,631] Patent No. 6,080,779, both cited above and incorporated herein by reference. For convenience, the isoprenoid pathway referred to is set forth herein in Figure 1.

Abstract: The present invention relates to c[C]ompounds that [inhibit the activity of NF-κB or]inhibit the activity of the proteasome or [both]the production of proteasomal proteins and promote [bone formation and]hair growth and are thus useful in [treating osteoporosis, bone fracture or deficiency, primary or secondary hyperparathyroidism, periodontal disease or defect, metastatic bone disease, osteolytic bone disease, post-plastic surgery, post-prosthetic joint surgery, and post-dental implantation; they also stimulate] the production of hair follicles and are thus useful in stimulating hair growth, including hair density, in subject where this is desirable.

In the Claims:

Please amend the following claims:

60. (Amended) The method of claim 45, wherein the compound is selected from the group consisting of



, pyrazylcarbonyl-Phe-Leu-Boronate (PS-341), tri-leucine vinyl sulfone (NLVS), N-carbobenzoyl-Ile-Glu-(OtBu)-Ala-Leu-CHO (PSI) epoxide, lactacystin and pentoxifylline(PTX).